DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

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Date: NOV 19 2003

From: Consumer Safety Officer, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-821

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: N-Acetyl-L-Hydroxyproline (AHYP)

Firm: Kyowa Hakko U.S.A., Inc.

Date Received by FDA: 02/21/03

90-Day Date: 05/23/03

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316.

Thank you for your assistance.

Susan C. Arthur
CSO/Lead Reviewer

Attachments

95S-0316

RPT176

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD

MAY - 6 2003

Mr. Neil Sullivan
Manager
Kyowa Hakko U.S.A., Inc.
599 Lexington Avenue, Suite 4103
New York, New York 10022

Dear Mr. Sullivan:

This is to inform you that the notification, dated February 14, 2003, you submitted pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on February 21, 2003. Your notification concerns the substance called "N-Acetyl-L-Hydroxyproline (AHYP)" that you intend to market as a new dietary ingredient.

The description of the dietary supplement states that the level of the new dietary ingredient within a supplement will be in the range of 50mg to 10mg per tablet or capsule. The conditions of use can be taken daily via oral administration with daily intake of not more than 300mg with single 50mg to 100mg oral doses taken three times per day.

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

The FDA has carefully considered the information in your submission and the agency has significant concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing AHYP will reasonably be expected to be safe.

You state in your submission that AHYP will be used at a level not to exceed 300 mg daily as a dietary supplement. The clinical data submitted in your notification cites several studies employing AHYP to relieve the symptoms and progression of various rheumatoid conditions in humans. Several of these studies identify adverse effects related to the use of AHYP, including

gastrointestinal side effects requiring discontinuation of the product. Notably, these studies, while asserting a more favorable tolerance profile of AHYP compared to other products it might be used as an alternative to, especially NSAIDs, do not address the possible complications or adverse outcomes which might occur with continued use of the product at the suggested dosage. Based on the adverse effects noted with the limited duration of use in these studies, a significant concern for more significant and serious adverse outcomes is raised with continued use of this product. As such, this information does not provide a reasonable basis of safety at the suggested dose.

The submission also includes one *in vivo* and two *in vitro* non-clinical studies. Only three animals/sex were used in the acute oral rat study. While two short-term (28-29 days) studies in rat and dog were briefly described in the submission, no actual data were provided. The available non-clinical data fail to support the safe use of N-Acetyl-L-Hydroxyproline.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that AHYP, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such an ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of February 21, 2003. After the 90-day date, May 24, 2003, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

Should you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-2375.

Sincerely,

For

Susan J. Walker, M.D.,
Acting Division Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling and
Dietary Supplements
Center for Food Safety and Applied Nutrition